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CLARK & ELBING LLP			SHAFER, SHULAMITH H	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<b>Office Action Summary</b>	<b>Application No.</b> 10/562,081	<b>Applicant(s)</b> VUOLTEENAHO ET AL.
	<b>Examiner</b> SHULAMITH H. SHAFER	<b>Art Unit</b> 1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 2/2/09.

2a) This action is FINAL.      2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 1-37, 40-44 and 46-60 is/are pending in the application.

4a) Of the above claim(s) 28-37 and 40-44 is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 1-27 and 46-60 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) Notice of References Cited (PTO-892)  
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)  
 3) Information Disclosure Statement(s) (PTO/SB/08)  
 Paper No(s)/Mail Date \_\_\_\_\_

4) Interview Summary (PTO-413)  
 Paper No(s)/Mail Date. \_\_\_\_\_

5) Notice of Informal Patent Application  
 6) Other: \_\_\_\_\_

**Detailed Action**

***Status of Application, Amendments, And/Or Claims:***

This Office Action is in response to amendment and remarks filed 2 February 2009.

Amendment to claims and specification, filed 2 February 2009 are acknowledged and entered. Claims 38, 39, and 45 are cancelled. Claims 1-18, 29, 24, 27, 29-31, 34 and 40-43 have been amended and the amendment made of record. Claims 46-60 are newly presented and made of record. Claims 1-37, 40-44, and 46-60 are pending in the instant invention. Claims 28-37 and 40-44 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-27 and 46-60 are under consideration to the extent they read on the elected invention.

***Priority:***

Acknowledgment is made of applicants' claim for foreign priority based on an application filed in United Kingdom on 30 June 2003. A certified copy of United Kingdom application 0315291.5 has been submitted with response of 2 February 2009. Therefore, the benefit of priority is granted to filing of United Kingdom 0315291.5, 30 June 2003.

**Withdrawn Objections/Rejections**

Claim 38 is cancelled rendering all objections and/or rejections to the claim moot.

***Withdrawn Objections:***

The objection to the title is withdrawn in light of Applicants' amendment to the title.

The objection to Claims 2-17 because of minor informalities is withdrawn in light of Applicants' amendment to the claims.

The objection to Claims 11 and 22 as failing to further limit the claims from which they depend is withdrawn in light of Applicants' persuasive arguments.

The objection to Claims 2, 3, 9, 18, 20, 24, 27, and 38 as having the incorrect format for sequence identifiers is withdrawn in light of Applicants' amendment to the claims.

***Withdrawn Rejections:***

The rejection of Claim 1 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, is withdrawn in light of Applicants' amendment to the claim.

The rejection of Claims 2, 3, 18, 24, 27 and 38 as vague and indefinite in utilizing the same Roman numerals in parts a and b of the claims is withdrawn in light of Applicants' amendment to the claim.

The following rejections under 35 U.S.C. 112, second paragraph are withdrawn in light of Applicants' persuasive arguments:

Claims 2, 4 and 38 as vague and indefinite in reciting "an oligospecific ... binding substance" or an "oligospecific antibody"

Claims 2, 3, 5, 18, 27 and 38 as vague and indefinite in reciting "homologous sequences"

Claim 8 as vague and indefinite in reciting "crossreacting polyclonal antibody"

Claim 13 as vague and indefinite in reciting "additionally comprises contacting the sample with a second binding substance....".

Claim 15 as vague and indefinite in reciting "wherein the second binding substance causes precipitation.....":

Claim 16 as vague and indefinite in reciting "an immunoassay"

The rejection of Claims 1-18, 21-27 and 38 under 35 U.S.C. 112, first paragraph, scope of enablement, is withdrawn in part, in light of Applicants' persuasive arguments. Issues still remaining are discussed below.

The rejection Claims 1-18, 21-27 and 38 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in part, in light of Applicants' persuasive arguments. Issues still remaining are discussed below.

Additionally, any objections or rejections not specifically maintained or presented in this Office Action is hereby withdrawn.

### **Maintained and/or New Objections and/or Rejections**

#### **Objections**

##### ***Claims:***

Claim 60 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The claim recites "The method of claim 49,....". Claim 49 is directed to the agent of claim 18; it is therefore directed to a product and not a method. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

#### **Rejections**

##### ***35 U.S.C. § 101:***

35 U.S.C. § 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The rejection of Claims 18, 19, and 22-24 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is maintained and now

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applied to newly submitted claims 49, 50, 56 and 57 for reasons of record and for reasons set forth below.

Claims 18, 19, and 22 are directed to an agent comprising a polypeptide comprising the N-terminal proANP and the N-terminal BNP. Newly submitted claims 49 and 56 are directed to species homologues or allelic variants of said peptides. The claims, as written do not sufficiently distinguish over a polypeptide that naturally exists in the organism because the claims do not particularly point out any non-naturally occurring differences between the claimed sequences and naturally occurring products.

Claims 23, and 24 are directed to a polynucleotide or an agent comprising a polynucleotide encoding the N-terminal proANP and the N-terminal BNP. Newly submitted claims 50 and 57 are directed to species homologues of allelic variants of said polynucleotides. The claims, as written do not sufficiently distinguish over a polynucleotide that naturally exists in the organism because the claims do not particularly point out any non-naturally occurring differences between the claimed sequences and naturally

Applicants traverse the rejection (Response of 2 February 2009, page 29, 3<sup>rd</sup> paragraph). The reason for the traversal is:

The claimed agents are synthetic, hybrid molecules including sequences from both proANP and proBNP (or their fragments and/or homologs). This is made clear in paragraphs [0218] - [0238] of the application publication (US 2007/0141634), which describe agents of the invention as including both proANP and proBNP-related sequences. ProANP and proBNP are encoded by different genes, and thus the claimed agents are not naturally produced.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

Applicants are arguing limitations not in the claims. It is noted that the features upon which applicant relies (i.e., the claimed agents are synthetic, hybrid molecules including sequences from both proANP and proBNP) are not recited in the rejected

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claim(s). Claim 18 and 19, from which claims 22, 49 and 56 ultimately depend are drawn to agents comprising proANP and proBNP polypeptides or fragments thereof. There is no recitation in the claims requiring these peptides to be linked together as fusion or chimeric proteins. Claims 22 and 23 from which claims 50 and 57 ultimately depend are drawn to polynucleotide comprising sequences which encode proANP and proBNP polypeptides. The claims do not require that the polynucleotides encode fusion or chimeric polypeptides. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

**35 U.S.C. § 112, Second Paragraph:**

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17,19, 20, 23, 24, 46-50, 52-56, 57, 59 and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps. The claim has been amended to recite "wherein detection of an increase in proANP and proBNP or fragments thereof, in the sample indicates activation of the ANP and BNP hormonal systems, and detection of a decrease in proANP and proBNP or fragments thereof, in the sample indicates inactivation of these systems". However, the claim does not recite a step indicating how one skilled in the art can conclude that the peptides of interest are increased or decreased (i.e. is one to compare values to a standard or control?). Thus, performing the steps of the claimed method would not achieve the stated goal, which is determining activation or inactivation of the atrial natriuretic peptide and brain natriuretic peptide hormonal systems by detecting the presence or amount of proANP and proBNP in a sample from the subject.

The rejection of Claim 3, which depends from Claim 1 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps is maintained for reasons of record. See MPEP § 2172.01. The claim is directed to a method of determining activation or inactivation of the atrial natriuretic peptide and brain natriuretic peptide hormonal systems by detecting the presence or amount of proANP and proBNP in a sample from the subject. The claim recites contacting the sample with an agent comprising both proANP and pro-BNP and contacting the sample with a binding substance which is able to bind to pro-ANP and proBNP. One of ordinary skill in the art would be unable to distinguish between the presence or amount of atrial and brain natriuretic peptide prohormones that are present in the sample as a result of activation or inactivation of the hormonal system as recited in claim 1, and the presence or amount of atrial and brain natriuretic peptide prohormones that are present in the sample as a result of contacting the sample with an agent comprising atrial and brain natriuretic peptide prohormones as recited in claim 3. While the claim recites contacting steps, it fails to explicitly recite method steps directed to **detection** of the atrial and brain natriuretic peptide prohormones that are present in the sample and distinguishing said peptides from the added agent. Thus, performing the steps of the claimed method would not achieve the stated goal, which is determining activation or inactivation of the atrial natriuretic peptide and brain natriuretic peptide hormonal systems by detecting the presence or amount of proANP and proBNP in a sample from the subject.

Applicants have not responded to this part of the rejection under 35 U.S.C. 112, second paragraph; the rejection is thus maintained.

The rejection of Claims 10 and 19 as being unclear as to whether applicants require that there be two sequences present is maintained for reasons of record and for reasons set forth below.

Applicants traverse the rejection (Response of 2 February 2009, Page 35, 2<sup>nd</sup> paragraph) The reason for the traversal are: the claims provide that the specified agent consists of one of seven (a-g) sequences that consist of the two indicated distinct sub-

sequences. That the sub-sequences are comprised within a single molecule is made clear in the description of agents of the invention in the application publication, such as in paragraphs [0218] - [0238].

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

Applicants are arguing limitations not recited in the claims. It is noted that the features upon which applicant relies (i.e., the specified agent consists of one of seven (a-g) sequences that consist of the two indicated distinct sub-sequences) are not recited in the rejected claim(s); the language of the claims do not unambiguously identify the agent as a protein comprising two linked sequences. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Additionally, Claims 10 and 19 are vague and indefinite in reciting "the agent comprises or consists of...". The transitional phrases "comprising" and "consisting of" define the scope of a claim with respect to what unrecited additional components, if any, are excluded from the scope of the claim. The transitional term "comprising" is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. The transitional phrase "consisting of" excludes any element, step, or ingredient not specified in the claim. *In re Gray*, 53 F.2d 520, 11 USPQ 255 (CCPA 1931); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) (MPEP 2111.03). Since these transitional phrases define very different compositions, it is unclear what applicants intend by reciting both of these phrases in the same claim.

The rejection of Claim 20 is maintained for reasons of record and for reasons set forth below. It is unclear how the SEQ ID NOs recited in claim 20 are related to the polypeptides recited in claim 19.

Applicants traverse the rejection (Response of 2 February 2009, page 35, 2<sup>nd</sup> paragraph). The reason for the traversal is:

Applicants note that the recited SEQ ID NOs:13, 14, 15, 17, 18, 19, and 20 correspond to the fusion peptides of parts a, b, c, d, e, f, and g of claim 19, respectively.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

Claim 20 does not recite the term "respectively"; thus the relationship between the sequences recited in claim 20 and the fragments identified in claim 19 is not specified and is unclear.

The rejection of Claim 23 as not clearly specifying what "a polypeptide" refers to is maintained for reasons of record and for reasons set forth below.

Applicants traverse the rejection (Response of 2 February 2009, page 35, last paragraph bridging page 36, 1<sup>st</sup> paragraph). The reason for the traversal is:

Claim 23 specifies a polynucleotide in relation to the polypeptide agent of claim 22, which is further defined by reference to claim 18. Claim 18 specifies an agent comprising a component from (a) and (b). As is made clear in paragraphs [0218] - [0238] of the application publication, agents of the invention include both proANP and proBNP-related sequences within a single molecule, so it is clear that the components in parts (a) and (b) of claim 18 are within a single molecule. Based on this, it is clear that the polypeptide of claim 23 includes within one molecule sequences from both proANP and proBNP which are, in particular, selected from the sequences listed in claim 18.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

Applicants are arguing limitations not recited in the claims. It is noted that the features upon which applicant relies (i.e., the polynucleotide of Claim 23 encodes a polypeptide that includes both proANP and proBNP related sequences within a single molecule) are not recited in the rejected claim(s); the language of the claim does not unambiguously identify the agent as a protein comprising two linked sequences, i.e. a

fusion protein. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim 47 is rejected as being incomplete for omitting essential steps (See MPEP § 2172.01). The claim is directed to a method of determining activation or inactivation of the atrial natriuretic peptide and brain natriuretic peptide hormonal systems by detecting the presence or amount of proANP and proBNP in a sample from the subject. The claim recites contacting the sample with an agent comprising both proANP and proBNP and contacting the sample with a binding substance which is able to bind to proANP and proBNP. One of ordinary skill in the art would be unable to distinguish between the presence or amount of atrial and brain natriuretic peptide prohormones that are present in the sample as a result of activation or inactivation of the hormonal system as recited in claim 1, and the presence or amount of atrial and brain natriuretic peptide prohormones that are present in the sample as a result of contacting the sample with an agent comprising atrial and brain natriuretic peptide prohormones as recited in claim 47. While the claim recites contacting steps, it fails to recite method steps drawn to **detection and determination of the amount** of the atrial and brain natriuretic peptide prohormones that are present in the sample, i.e., detection followed by estimating the amount present in the sample by comparing the values obtained in the method to a control or a standard and distinguishing said peptides from the added agent. Thus, performing the steps of the claimed method would not achieve the stated goal, which is determining activation or inactivation of the atrial natriuretic peptide and brain natriuretic peptide hormonal systems by detecting the presence or amount of proANP and proBNP in a sample from the subject.

Claims 47 and 59 are vague and indefinite in reciting "a first binding substance which is able to bind to : (c) (i), (ii), (iii), (iv) **and/or** (d) (i), (ii), (iii), (iv). It is unclear how one is to detect both pro-ANP and pro-BNP in the sample if the binding substance is to bind to a proANP **or** a proBNP.

Claim 49 is vague and indefinite in reciting "An agent... which comprises both proANP and prBNP". It is unclear if the agent comprises two individual peptides or one polypeptide sequence comprising sequences of both polypeptides linked together.

Claim 52 is vague and indefinite. It is unclear if the binding substance recited in the claim is to bind to the homologous sequence of (a)(iii) and the peptide of (a)(i) or (a)(ii) and the homologous sequence of (b) (iii) and the peptide of (b) (i) or (b) (ii), or one sequence listed under section (a) and one sequence listed under (b), that is, does the binding substance bind to two peptides or four peptides?

Claim 60 is vague and indefinite in reciting "The method of claim 49...". Claim 49 is directed to an agent, which is a product and not to a method. Since it is unclear what the claim is directed to, it will not be examined any further as to its merits.

### ***35 U.S.C. § 112, First Paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

### ***Enabling***

Claims 1-6, 9-17, 46-48, 52-55 and 59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining activation of the ANP and BNP hormonal system, the method comprising simultaneously detecting the presence or amount of atrial and brain natriuretic peptide prohormones or fragments thereof which comprises:

Contacting the sample with a bi-or oligospecific first binding substance wherein said binding substance is an antibody or antigen binding fragment thereof  
said binding substance being able to bind to both

a) (i) proANP (SEQ ID NO:1), ANP (SEQ ID NO:2) or NT-proANP (SEQ ID NO:3)  
(ii) a species homologue or allelic variant of (a) (i) , (iii) a homologous sequence having at least 70%, 75%, 80%, 90%, 95%, 97% or 99% identity to (a) (i) or (a) (ii) or a fragment of (a)(i) (ii) or (iii) thereof which is at least 6 amino acids in length and  
b) (i) pro-BNP (SEQ ID NO:4), BNP (SEQ ID NO:5) or NT-proBNP (SEQ 1D NO:6) (b)(ii) a species homologue or allelic variant of (b) (i),(b)(iii) a homologous sequence having at least 70%, 75%, 80%, 90%, 95%, 97% or 99% identitiy to (b)(i) or (b) (ii) or a fragment of (b)(i) (ii) or (iii) thereof which is at least 6 amino acids in length or a method comprising

contacting the sample with a bi- or oligospecific first binding substance wherein said binding substance comprises SEQ ID NOs:33 (natriuretic receptor GC-A) or 34 (extracellular binding domain of the natriuretic receptor GC-A) said binding substance being able to bind to both

a) (i) proANP (SEQ ID NO:1), ANP (SEQ ID NO:2) or NT-proANP (SEQ ID NO:3) or (ii) a homologous sequence having at least 95%, 97% or 99% identity to (a) (i) and  
b) (i) pro-BNP (SEQ ID NO:4), BNP (SEQ ID NO:5) or NT-proBNP (SEQ 1D NO:6) or (ii) a homologous sequence having at least 95%, 97% or 99% identity to (b) (i) followed by comparing the detected amount in the sample to a control or a standard, thereby concluding that the amount of said hormones is higher or lower than the required normal amounts,

does not reasonably provide enablement for a method comprising simply contacting the sample with a first binding substance with wherein the first binding substance comprises a homologous sequence having at least 70% identity to SEQ ID NO:33 or a fragment of SEQ ID NO:33 or a fragment of a homologous sequence having at least 70% identity to SEQ ID NO:33 which is at least 400 amino acids in length or an extracellular binding domain of the natriuretic receptor GC-A (SEQ ID NO:34) said binding substance able to bind to both

A(i) a species homologue or allelic variant of proANP (SEQ ID NO:1), ANP (SEQ ID NO:2) or NT-proANP (SEQ ID NO:3, or A(ii) a homologous sequence having at least

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70%, 75%, 80%, 90%, identity to (A) (i) or (A) (iii) or a fragment of (A)(i) (ii) thereof which is at least 6 amino acids in length and

B(i) a species homologue or allelic variant of proBNP (SEQ ID NO:4), BNP (SEQ ID NO:5) or NT-proBNP (SEQ ID NO:6), or B(ii) a homologous sequence having at least 70%, 75%, 80%, 90%, identity to (B) (i) or (B) (iii) or a fragment of (B)(i) (ii) thereof which is at least 6 amino acids in length and

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

This rejection is being maintained for reasons of record and for reasons set forth below.

The claims are broadly drawn to a method comprising contacting the sample with a binding substance that binds to both a species homologue or variant of proANP or a homologous sequence having at least 70%, 75%, 80%, 90%, 95%, 97% or 99% identity to proANP or a fragment of thereof which is at least 6 amino acids in length and a species homologue or variant of proBNP or a homologous sequence having at least 70%, 75%, 80%, 90%, 95%, 97% or 99% identity to proBNP or a fragment thereof which is at least 6 amino acids in length. The binding substance, as recited in Claims 5 and 6 may be a natriuretic receptor of SEQ ID NO:33 or the extracellular binding domain of said receptor (SEQ ID NO:34).

Thus, the claims encompass utilizing variant receptors as binding substances to bind variant polypeptides and fragments thereof.

The full scope of the claims is not enabled for the following reasons.

Variant Polypeptides: The specification teaches polypeptides which are the homologous or allelic variants having at least 70% identity to the disclosed sequences and/or the fragments thereof that comprise at least 6 amino acids in length. [paragraph 0178 of PGPUB 20070141634, the PGPUB of the instant invention]. However, insufficient guidance is presented as to which portions of the polypeptides must be preserved in order to retain the ability to bind to the binding substance wherein the

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binding substance is a receptor. One of skill in the art would be aware that specific amino acids must be retained in order to enable the ligand to make contact and bind to its cognate receptor. However, the specification has not disclosed what portions of the ANP (SEQ ID NO:3, the elected species) and the BNP (SEQ ID NO:6, the elected species) polypeptides which are sequences of 98 and 76 amino acid residues, respectively, must be present to enable binding to the receptor. Applicants have not disclosed any structural requirements for retaining the functional characteristic of binding to the cognate receptor.

Variant Binding substances: The specification teaches that such a binding substance may comprise a receptor or fragments thereof. The first binding substance may comprise: (a) natriuretic receptor GC-A (SEQ ID NO: 33), GC-B (SEQ ID NO: 35) or GC-C (SEQ ID NO: 36), homologous variants of said sequences and fragments thereof. The first binding substance may also comprise an extracellular binding domain of the natriuretic receptor GC-A (SEQ ID NO: 34) or a homologous variant or fragment thereof. [paragraphs 0190-0193]. The claims require that these binding substances, which comprise receptors or the extracellular domains thereof, retain the ability to bind ANP and BNP. However, the disclosure presents insufficient guidance as to which portions of the natriuretic receptor of SEQ ID NO:33 or its extracellular domain must be preserved in order for the required biological activity, binding activity be retained. The specification has not taught any specific structural requirements that must be maintained in order that the variant receptors or extracellular domains thereof retain the functional characteristic of binding to its cognate ligand.

Applicants traverse the rejection (Response of 2 February 2009, page 38, last paragraph bridging page 40, 1<sup>st</sup> paragraph). The reasons for the traversal are:

1. the application describes variants of the binding substance targets, agents, and corresponding polynucleotide sequences of the present claims, and that these variants could be made and tested using standard methods in the art.
2. With respect to proANP and proBNP related sequences (such as sequences having at least 70% identity to proANP, proBNP, and fragments thereof) to which a first

binding substance binds, those of skill in the art could readily prepare sequences having this level of identity, and then prepare a binding substance (such as an antibody) that binds to the sequences. Making antibodies that bind to proteins is standard in the art, and Applicants respectfully submit that undue experimentation would not be required to make such antibodies. As to using them in methods to determine activation or inactivation of ANP and BNP hormonal systems, Applicants submit that the binding substances could readily be tested to determine whether they bind to proANP and proBNP-related sequences in samples in the same manner as binding substances directed against proANP and proBNP sequences that are naturally present in patient samples.

3. Activities that are relevant to the variants specified in the present claims are binding activities, such as assays for detecting binding between a binding substance, such as an antibody, and a target including particular amino acid sequences. Applicants submit that it is well known in the art that identifying a binding substance that binds to a variant peptide, while perhaps requiring trial and error experimentation, is generally feasible using standard methods.

Applicant's arguments have been fully considered and have been found to be persuasive in part. Thus, the enablement rejection as applied to binding substances wherein the binding substance is an antibody has been withdrawn. The Examiner agrees that one of ordinary skill could generate antibodies to fragments of ANP and/or BNP and test said antibodies for binding to specific fragments or variants.

However producing variant *receptors* and testing such variant receptors to determine which would bind to variant ligands or fragments of said ligands would require undue experimentation.

One of ordinary skill in the art would be unable to predict which fragments of the receptor would bind to its cognate ligand and which fragments of ANP or BNP would bind to its cognate receptor without additional guidance. Without specific information as to which amino acid residues of the receptor (binding domain) must be maintained to

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retain the ability to bind a cognate ligand, and which amino acids of the ANP or BNP sequences must be retained to enable the ligand to bind to its cognate receptor, one of ordinary skill would have to undertake undue experimentation to practice the claimed invention in its full scope.

***Written Description***

The rejection of Claims 1-6, 9-17, 24 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. is maintained and applied to newly submitted claims 46-48, 50, 52-55 and 59. The claim (s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to assays utilizing binding substances comprising homologous sequences having at least 70% identity to SEQ ID NO:33 and fragments thereof which are at least 400 amino acids in length or the extracellular domain of natriuretic receptor GC-A (SEQ ID NO:34). The claims are also drawn to polynucleotides which hybridize to nucleic acids of SEQ ID NOs 7-12. Thus, the claims are drawn to a genus of nucleic acids that is defined by only by hybridization ability and methods utilizing a genus of receptors having at least 70% identity to SEQ ID NO:33 or fragments thereof which are at least 400 amino acids in length.

Claims 24 and 50 encompass a genus of nucleic acids that hybridize under medium or high stringent conditions to SEQ ID NOs:7-12, species homologues or allelic variants thereof or sequences complementary to the recited sequences. One of ordinary skill in the art would recognize that even under conditions of high stringency, a significant degree of mismatch occurs. Thus, hybridization under high or medium stringency would result in a myriad of nucleic acids which are not further described. Additionally, without a recognized correlation between structure and function, one of ordinary skill would not be able to identify without further testing which of those nucleic

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acids that hybridize to the recited sequences would also encode a polypeptide that binds to the recited binding substance, particularly the receptor of SEQ ID NO:33 or 34. Thus one would not conclude that the applicants are in possession of the claimed genus of nucleic acids.

Additionally, the claims are drawn to utilizing variant receptors to bind variant polypeptides. In the absence of teachings as to recognized correlation between structure and function (which amino acids of the variant receptor are required to bind a cognate ligand and which amino acids of variant polypeptides are required to bind to cognate receptor), one would conclude that the specification does not provide written description of the claimed genus: a genus of receptors having at least 70% identity to SEQ ID NO:33 or fragments thereof which are at least 400 amino acids in length.

Applicants traverse the rejection (Response of 2 February 2009, page 41, 2<sup>nd</sup> paragraph bridging page 43, 2<sup>nd</sup> paragraph). The reasons for the traversal:are:

1. With respect to the sequences specified in the method claims, the sequences must bind to the first binding substance in a manner that is similar to or can be compared with the binding of the first binding substance to the corresponding reference sequence as specified in claim 2. These binding features, when combined with the partial structure information, provide ample written description of the present claims.

2. The specification provides information concerning conserved structures of the peptides of the present claims. The disclosure provides several examples of peptides to which binding substances of the invention may bind. It is generally feasible using standard methods to obtain a binding substance, such as an antibody, that binds to the variant.

Applicant's arguments have been fully considered and have been found to be persuasive in part. Thus the written description rejection to methods utilizing antibodies binding to homologous sequences, variants and fragments of ANP and/or BNP has been withdrawn.

However, the rejection as applied to methods using variants of the natriuretic receptor to bind proANP and proBNP or variants thereof, and polynucleotides described solely by hybridization ability is maintained for reasons of record and reasons stated above.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 115).

**35 U.S.C. § 103:**

Claims 10, 19 and 49 are drawn to agents comprising proANP and proBNP. It is the examiner's position that the claims do not require that these peptides be linked; the claims as written, are interpreted as drawn to agents which comprise both proteins as individual protein sequences.

Claims 24, 25, 26, 27, 50, 51 are drawn to polynucleotides encoding proANP and proBNP. It is the examiner's position that the claims do not require that these polynucleotides encode peptides that are linked (for example, fusion proteins); the claims as written, are interpreted as drawn polynucleotides which encode agents which comprise both proteins as individual protein sequences.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of Claims 1, 16 and 17 under 35 U.S.C. 103(a) as being unpatentable over Clerico et al (1998. J Endoc. Invest 21:170-179, in view of Clerico et al. (2000. Clin. Chemistry 46:1529-1534) is maintained for reasons of record and for reasons set forth below.

Clerico et al (1998) teach measurement of plasma atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels in plasma of patients with heart failure as an assay method useful in follow-up of cardiac patients (monitoring a cardiac condition). The measurements were performed using non-competitive immunoradiometric assays (IRMA). Clerico et al (1998) does not teach a method comprising detecting the presence of atrial and brain natriuretic peptide prohormones or fragments thereof. Clerico et al (2000) teach that cardiac natriuretic hormones are a family of related peptides including ANP, BNP and other peptides derived from the N-terminal portion of proANP and proBNP peptide chains. The reference teaches that the N-terminal prohormones are present in greater amounts in the plasma than ANP and BNP.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the methods taught by Clerico et al (1998) and substitute measurement of proANP and proBNP (as taught by Clerico et al (2000)) for the measurement of ANP and BNP as taught by Clerico et al. (1998). The person of ordinary skill in the art would have been motivated to make these modifications and anticipate success because Clerico et al (2000) teach that the prohormones are present in higher concentrations in the plasma and one of ordinary skill in the art would recognize that these may be measured more easily and accurately. Applicants traverse the rejection (Response of 2 February 2009, page 43, last paragraph, bridging page 45, 1st paragraph). The reasons for the traversal are:

1. the invention is drawn to detection of *both* proANP and proBNP-related sequences at the *same time*, in the *same test reaction*, yielding a *single test result*.
2. Clerico (1998) teaches detection of ANP and BNP in separate reactions, using separate test kits; the reactions were clearly carried out in separate reactions, using separate kits and reagents, and resulting in two sets of results.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

One of ordinary skill in the art, aware that it is routine to detect multiple compounds in a single sample at the same time in the performance of clinical assays

(for example, a lipid profile, liver enzyme assays), would be motivated to assay both ANP and BNP in the same assay to increase the efficiency and reduce the costs of said assays. Absent evidence that assaying for one protein, i.e. detection of ANP, would interfere with the detection of the second protein, i.e. detection of BNP, one of ordinary skill would anticipate success in detecting both proteins simultaneously in the same sample. The rejection is thus maintained.

As previously stated, the Examiner has interpreted claims 3, 4 and 9-11 to be directed to a competitive binding assay, such as a radioimmunoassay.

The rejection of Claims 2-4, 7-15 under 35 U.S.C. 103(a) as being unpatentable over Clerico et al (1998) in view of Clerico et al. (2000) as applied to claim 1 further in view of Buechler et al (US 7,341,838, filed 19 April 2004, priority claimed to provisional application 60/466,358, filed 28 April 2003, the '838 patent) is maintained and now applied to newly submitted claims 46, 47, 52-54 and 59 for reasons of record and for reasons set forth below.

The teachings of Clerico et al (1998) and Clerico et al (2000) are outlined in detail above. In addition to the teachings above, Clerico et al. (2000) teach competitive assays such as radioimmunoassays comprising labeled antigens such as ANP and BNP, thus teaching agents comprising proANP and proBNP (as required by claims 3, and 47). The references, singly or in combination, do not teach the further limitations of:

A method of claim 1 which comprises contacting the sample with an agent comprising both SEQ ID NO:3 and SEQ ID NO:6 and a first binding substance which is able to bind to SEQ ID NO:3 and SEQ ID NO:6 (newly submitted Claim 47) or

contacting the sample with a bi- or oligo-specific binding substance that is able to bind to both NT-proANP of SEQ ID NO:3 and NT-proBNP of SEQ ID NO:6 (Claims 2, 3 and newly submitted claims 46 and 59) or

wherein the first binding sequence binds to both a homologous sequence or fragments of proANP and a homologous sequence or fragments of proBNP (Claim 52) or

wherein the homologous sequence or fragment of proANP and the homologous sequence or fragment of proBNP is capable of binding to the binding sequence that binds to SEQ ID NO:3 and SEQ ID NO:6 (claims 53 and 54), or

wherein the binding substance comprises an antibody that binds to NT-proANP of SEQ ID NO:3 and NT-proBNP (SEQ ID NO:6) (Claims 7 and 8),

wherein the first binding substance or agent is labeled and/or immobilized (claim 12) or

a method which additionally comprises contacting the sample with a second binding substance which is able to bind to the first binding substance, wherein the second binding substance is labeled or immobilized and wherein a precipitate is formed (claims 13-15)

The '838 patent teaches a sequence (SEQ ID NO:3) comprising a segment, amino acids 1-98, which is 99.4% identical to SEQ ID NO:3 of the instant invention and is identified as an ANP precursor, pro-ANP (pro-hormone). The reference also teaches a sequence, SEQ ID NO:1, comprising a segment, amino acids 1-76 which is 100% identical to SEQ ID NO:6 of the instant invention and is identified as a BNP-precursor molecule (pro-hormone). One of ordinary skill in the art would recognize that antibodies which recognize polypeptides comprising segments 99.4% and 100% identical to SEQ ID NO:3 and SEQ ID NO:6, respectively, of the instant invention would recognize the polypeptides of the instant invention. Absent evidence to the contrary, these antibodies would also recognize homologous sequences or fragments of SEQ ID NO:3 and SEQ ID NO:6 (as recited by claims 52-54 and 56). The '838 patent teaches measuring fragments in samples; said fragments could be pro-ANP and pro-BNP (column 15, lines 36-43). The fragments are recognized by antibodies. Said antibodies may comprise bivalent antibodies, comprising two Fab fragments linked by a disulfide bridge at the hinge region (column 16, lines 21-23), thus teaching a bispecific binding substance that binds to proANP and proBNP, as required by claims 2, 3, 7, 46, 47, and 59). The antibodies may be monoclonal antibodies or polyclonal antibodies (column 16, lines 34-39), as required by claim 8. The reference teaches immunoassays comprising a tagged antibody (column 18, lines 24-26), a limitation of claim 12. The '838 patent teaches

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immunoassays comprising labeled antimmunoglobulin antibodies (column 18 lines 53-55), thus meeting the limitations of claims 13 and 14. The reference also teaches "capture" or "sandwich" ELISA wherein the antigen-antibody-2<sup>nd</sup> antibody complex precipitates (column 18, line 60 bridging column 19, line 3) and radioimmunassays (column 18, lines 32-55).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the methods taught by Clerico et al (1998) and Clerico et al (2000) and substitute the polypeptides of SEQ ID NOs: 3 and 1 as taught by the '838 patent for the generic proANP and pro-BNP taught by the Clerico et al (2000) and utilize the antibodies and immunoassays taught by the '838 patent in place of the IRMA assays taught by Clerico et al (1998). The person of ordinary skill in the art would have been motivated to make these modifications because the '838 patent identifies the polypeptides of SEQ ID NOs:3 and 1 as proANP and pro-BNP and one of skill in the art would recognize that one may use bivalent antibodies to bind to different antigens, antibodies directed to the full length sequence would also bind homologous sequences or fragments of said sequences and that different types of immunoassays (RIAs, IRMAs and ELISAs) are art-recognized equivalents. One would reasonably have expected success because methods of making bivalent antibodies for use in diverse immunoassays and methods of practicing different immunoassays are well known in the art.

Applicants traverse the rejection (Response of 2 February 2009, page 45, 2<sup>nd</sup> paragraph, bridging page 46, 2nd paragraph). The reasons for the traversal are:

1. The present invention is the simultaneous detection of both proANP and proBNP-related sequences in a single assay, to obtain a single result. The methods of Clerico involve the use of two separate assays for separate detection of ANP and BNP-related sequences, resulting in more than one result.
2. Buechler ('838) does not teach or suggest testing for both proANP and proBNP-related sequences at the same time, in a single assay, to obtain a single result.

Applicant's arguments have been fully considered but are not found to be persuasive for reasons cited above and reiterated below:

One of ordinary skill in the art, aware that it is routine to detect multiple compounds in a single sample at the same time in the performance of clinical assays, would be motivated to assay both ANP and BNP in the same assay for to increase the efficiency and reduce the costs of said assays. Absent evidence that assaying for one protein, i.e. detection of ANP, would interfere with the detection of the second protein, i.e. detection of BNP, one of ordinary skill would anticipate success in detecting both proteins simultaneously in the same sample. The '838 patent is cited to teach sequences of ANP and BNP identical to those recited in the claims of the instant invention. The rejection is thus maintained.

The rejection of Claims 5 and 6 under 35 U.S.C. 103(a) as being unpatentable over Clerico et al (1998) in view of Clerico et al. (2000) and Buechler et al (the '838 patent) as applied to Claims 1 and 2 and further in view of Bentivegna et al. (WO 01/79231, the '231 reference) is maintained and is applied to newly submitted claims 48 and 55. The teachings of Clerico et al (1998), Clerico et al (2000), and the '838 patent are outlined in detail above. The references, singly or combined, do not teach the further limitations of a method wherein the binding substance comprises the natriuretic receptor GC-A (SEQ ID NO:33), as recited in claims 5 and 48 or comprises an extracellular binding domain of the natriuretic receptor GC-A (SEQ ID NO:34) as recited in claim 6 or wherein the homologous sequence with 97% or 99% identity to SEQ ID NO: 33 is capable of binding to a second binding substance with also binds to SEQ ID NO:33, as recited in claim 55. The '231 reference teaches a sequence, SEQ ID NO:3, which is 100% identical to SEQ ID NO:33 of the instant invention. This sequence comprises a domain, the extracellular ligand binding domain, that is 100% identical to SEQ ID NO:34 of the instant invention. The reference identifies the sequence as the human NPR1 (receptor) polypeptide, which is recognized in the art as the natriuretic receptor or NPR-A) which comprises an extracellular natriuretic peptide-binding domain which binds both ANP and BNP. One of ordinary skill in the art would recognize that a homologous sequence of 97% or 99% identity to SEQ ID NO: 33 would exhibit the same binding characteristics of a protein of SEQ ID NO:33.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the methods taught by Clerico et al (1998) Clerico et al (2000) and the '838 patent and substitute the receptor taught by the '231 reference, which binds both BNP and ANP for the antibodies which bind BNP and ANP (taught by Clerico et al (1998) Clerico et al (2000) and the '838 patent) in the methods of the instant invention. The person of ordinary skill in the art would have been motivated to make these modifications and reasonably have expected success because one of ordinary skill in the art would recognize that both receptors comprising extracellular ligand binding domains and antibodies may be used to bind antigens such as ANP and BNP and would thus be art accepted equivalents.

Applicants traverse the rejection (Response of 2 February 2009, page 47, 2<sup>nd</sup> paragraph). The reasons for the traversal are:

None of the cited references, alone or in combination, provide any teaching or suggestion of a central feature of the present invention, which is the simultaneous detection of both proANP and proBNP-related sequences in a single assay, giving rise to a single result.

Applicant's arguments have been fully considered but are not found to be persuasive for reasons cited above and reiterated below:

One of ordinary skill in the art, aware that it is routine to detect multiple compounds in a single sample at the same time in the performance of clinical assays, would be motivated to assay both ANP and BNP in the same assay to increase the efficiency and reduce the costs of said assays. Absent evidence that assaying for one protein, i.e. detection of ANP, would interfere with the detection of the second protein, i.e. detection of BNP, one of ordinary skill would anticipate success in detecting both proteins simultaneously in the same sample. The rejection is thus maintained.

The rejection of Claims 18- 22 under 35 U.S.C. 103(a) as being unpatentable over Nakata et al. (2001. EP1 118 329 A1) in view of Buechler et al (the '838 patent) is maintained and applied to newly submitted claims 49 and 56 for reasons of record and

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reasons set forth below. Nakata et al teach compositions comprising natriuretic peptides including ANP and BNP; the reference teaches that ANP and BNP having different structures (prohormones, fragments) are known and the natriuretic peptides in compositions taught by Nakata et al include all of them [paragraph 0010]. Thus, the compositions taught by Nakata et al. encompass an agent comprising ANP and BNP, prohormones and fragments thereof. Nakata et al do not teach agents comprising a sequence having at least 70% identity to SEQ ID NO:3 (NT-proANP) and a NT-proBNP of SEQ ID NO:6 or an agent comprising proBNP1-108 and proANP1-126 which comprises SEQ ID NO:19 or an homologous sequence of ANP or BNP which is capable of binding to a binding substance which also binds to SEQ ID NO:3 or SEQ ID NO:6. As stated above, the '838 patent teaches polypeptides which comprise sequences comprising segments that are 99.4% and 100% identical to SEQ ID NO:3 and SEQ ID NO:6, respectively. One of ordinary skill in the art would recognize that a homologous sequence of 97% or 99% identity to SEQ ID NO:3 or SEQ ID NO:6 would exhibit the same binding characteristics of SEQ ID NO:3 or 6, as recited in claim 56. The '838 patent also teaches sequences comprising proBNP1-108 (SEQ ID NO:1 disclosed in the '838 patent) and a proANP1-126 (SEQ ID NO:3 disclosed in the '838 patent).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Nakata et al. and substitute the polypeptides comprising segments of SEQ ID NOs: 3 and 1 or sequences comprising proBNP1-108 and proANP1-126 as taught by the '838 patent for the generic ANP and BNP and ANP and BNP peptides having different structures as taught by Nakata et al. The person of ordinary skill in the art would have been motivated to make these modifications because the '838 patent identifies the polypeptides of SEQ ID NOs:3 and 1 as proANP and pro-BNP. Additionally, it would be obvious to one of skill in art to make a fusion protein comprising proBNP1-108 and proANP1-126 comprising SEQ ID NO: 1 and SEQ ID NO:3 taught by the '858 protein to arrive at a fusion protein of SEQ ID NO:19 of the instant invention, which comprises as amino acids 1-108 a sequence which is 100% identical to SEQ ID NO:1 of the referenced patent and as amino acids 109-234 a sequence which is 99.2% identical to SEQ ID NO:3 of the referenced patent

The one amino acid difference comprises the conservative substitution of aspartic acid for glutamic acid (both being acidic amino acids; one of skill in the art would predict that this would not change the biological activity of the the fusion protein). One would be motivated to make said fusion protein so that one could have a protein comprising equimolar amounts of pro-BNP and pro-ANP to use as a standard in immunoassays using bivalent antibodies (as disclosed by the '838 patent) to detect both proteins. One would have a reasonable expectation of success because methods of making fusion proteins are well known in the art.

Applicants traverse the rejection (Response of 2 February 2009, page 47, last paragraph bridging page 48, last paragraph). The reasons for the traversal are:

1. The proANP and proBNP related sequences in the agent are part of the same molecule.
2. there is no teaching or suggestion in the cited references to make fusion proteins or other molecules including both proANP and proBNP-related sequences, as is required by the present claims.
3. there is no teaching or suggestion of detecting both proANP and proBNP-related sequences in the cited references, and there is also no teaching or suggestion to make the fusion proteins noted by the Examiner.

Applicant's arguments have been fully considered but are not found to be persuasive for reasons set forth below:

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the claimed agents are synthetic, hybrid molecules including sequences from both proANP and proBNP) are not recited in the rejected claim(s) 18, 19, 21 and 22. Claim 18 and 19, from which claims 21 and 22, depend are drawn to agents comprising proANP and proBNP polypeptides or fragments thereof. There is no recitation in the claims requiring these peptides to be linked together as fusion or chimeric proteins.

One of ordinary skill in the art, aware that it is routine to detect multiple compounds in a single sample at the same time in the performance of clinical assays,

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would be motivated to assay both ANP and BNP in the same assay to increase the efficiency and reduce the costs of said assays. Absent evidence that assaying for one protein, i.e. detection of ANP, would interfere with the detection of the second protein, i.e. detection of BNP, one of ordinary skill would anticipate success in detecting both proteins simultaneously in the same sample.

While there is no teaching in the cited arts to construct fusion proteins, as cited above, one of ordinary skill would recognize the advantages of generating such fusion proteins so that one could have a protein comprising equimolar amounts of pro-BNP and pro-ANP to use as a standard in immunoassays using bivalent antibodies (as disclosed by the '838 patent) to detect both proteins. The rejection is thus maintained.

The rejection of Claims 23-27 under 35 U.S.C. 103(a) as being unpatentable over Lewicki et al (the '286 patent) and Simari (WO 00/71576, the '576 reference) is maintained and applied to newly submitted claims 50, 51, 57 and 58 for reasons of record and for reasons set forth below.

The '286 patent teaches a sequence, SEQ ID NO:3, comprising a sequence that is 100% identical to SEQ ID NO:9 of the instant invention; the reference teaches this nucleotide sequence as encoding an atrial natriuretic peptide. The reference teaches expression vectors (for example, column 6, lines 3-18, column 71, line 25) host cells (column 82, lines 46-54), and methods of making the protein of interest recombinantly (column 13, lines 38-42, and column 82, lines 46-54).

The '576 reference teaches a sequence comprising a sequence that is 100% identical to SEQ ID NO:12 of the instant invention. This sequence is described as encoding a natriuretic peptide, BNP, useful to inhibit or prevent heart failure. The reference teaches plasmids (page 7, 5<sup>th</sup> paragraph, Figure 3) and host cells expressing the protein of interest and methods of isolating recombinantly produced protein (page 7, 6<sup>th</sup> paragraph, Figure 4)

In addition to the teachings above, the '286 patent teaches that compounds of the disclosed invention (polypeptides encoded by the disclosed nucleotide sequences) may be mixed with, bonded to or conjugated with compounds having the same or a

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complementary range of biological activities. One of skill in the art would recognize that both ANP and BNP have potent diuretic, natriuretic, and vascular smooth muscle-relaxing effects and the advantages of utilizing a composition comprising nucleic acids which encode proteins having the same or a complementary range of biological activities to efficiently produce said proteins recombinantly.

Furthermore one of ordinary skill in the art would recognize that a sequence which encodes a sequence having at least 95%, 97% or 99% identity to SEQ ID NO:9 or SEQ ID NO:12 would encode a sequence having the same binding characteristics as those encoded by SEQ ID NO:9 or SEQ ID NO:12.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of the '286 patent and the '576 reference to produce a composition comprising the nucleotides disclosed in each of the references. The person of ordinary skill in the art would have been motivated to make these modifications and anticipate success because the '286 patent teaches that compounds of the disclosed invention (polypeptides encoded by the disclosed nucleotide sequences) may be mixed with, bonded to or conjugated with compounds having the same or a complementary range of biological activities, and thus it would be advantageous to have a composition comprising polynucleotides encoding both ANP and BNP in order to efficiently produce said polypeptides recombinantly, since the art teaches both polypeptides have potent diuretic, natriuretic, and vascular smooth muscle-relaxing effects.

Applicants traverse the rejection (Response of 2 February 2009, page 49, last paragraph bridging page 50). The reasons for the traversal are:

Simari concerns mixing together or conjugation of polypeptides, not polynucleotides. There is no teaching that even if sequences of pro-ANP and pro-BNP related sequences were produced in a fusion protein, they would have the biological activities of interest. The present claims specify polynucleotide molecules encoding proteins including proANP and proBNP-related sequences. There is no teaching or

suggestion in the Lewicki ('286) and Simari ('576) references of such proteins or polynucleotides encoding them.

Applicant's arguments have been fully considered but are not found to be persuasive for reasons set forth below:

As noted above, the claims do not unambiguously recite polynucleotides encoding fusion proteins comprising proANP and proBNP. The claims are directed to polynucleotides encoding said proteins. One could interpret the claims as reciting polynucleotides encoding separate sequences. One of ordinary skill would be motivated to produce compositions comprising said polynucleotides as said polynucleotides could be used to efficiently produce both proANP and proBNP. One would be motivated to produce compositions comprising both of these polypeptides, as Simari teaches the advantages of compositions comprising compounds having the same or complementary biological activities.

**Conclusion:**

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHULAMITH H. SHAFFER whose telephone number is (571)272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao, Ph.D. can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. H. S./  
Examiner, Art Unit 1647

/Manjunath N. Rao, /  
Supervisory Patent Examiner, Art Unit 1647